# Regio- and Stereospecific $Me_3SiI$-Promoted Intramolecular Displacement of Hydroxy Group by Sulfide. 2. Polyhydroxylated Thiepane Ring Contraction to Thiolane or Thiane Derivatives. Synthesis of Enantiopure Polyalcohols[1]

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## Introduction

A well-known characteristic of medium-sized rings (8−11-membered) is their ability to undergo facile transannular reactions.[2] Evidence has been found that transannular interactions involving sulfide sulfur may already take place in seven-membered rings.[3] We have recently described[1] a facile reaction which occurs, in high yield, in the presence of trimethylsilyl iodide, on $\delta$ and $\epsilon$ hydroxy or alkoxy sulfides by intramolecular displacement of the oxygen functionality with formation of cyclic sulfonium salts. A transannular version of this reaction, applied to 4-hydroxythiepane, resulted in the facile ring contraction of a 7-membered to a 5-membered cyclic sulfide to give exclusively 2-(2-iodoethyl)tetrahydrothiophene in high yield. It is of interest that $Me_3SiI$ is compatible with a variety of functional groups, including multiple carbon−carbon bonds, ketones, amines, and aromatic halides.[4] We have also pointed out that the cyclization with $Me_3SiI$ is an intramolecular $S_N2$ reaction.[1]

Through these findings, we envisaged a route to synthesize, on a multigram scale, enantiopure thiosugar analogues from inexpensive sugars.

## Results and Discussion

In this paper we report the transannular cyclization of *trans*-4,5-dihydroxythiocane (**1**),[5] promoted by $Me_3SiI$ generated *in situ*. As expected, for an intramolecular $S_N2$ reaction, only one product, *exo*-4-hydroxy-*cis*-thioniabicyclo-[3.3.0]octane iodide (**2**), was obtained (Figure 1). The product, obtained with this new procedure, proved identical in all respects to the one synthesized previously[6] by transannular cyclization of **1** under acidic conditions.

It is easy to predict that the reaction with $Me_3SiI$ occurs stereospecifically and with complete configurational inversion if the sulfur attacks a chiral carbon bearing a hydroxy group.

These results therefore allow for the possibility of utilizing a simple synthetic approach to bicyclic[3.3.0] hydroxylated sulfonium salts derived from 8-membered

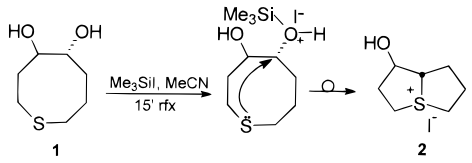


**Figure 1.**

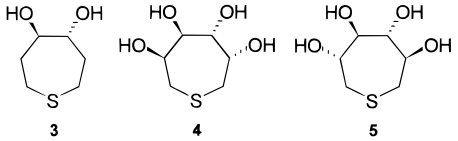


**Figure 2.**

cyclic sulfides. In particular, thio analogues of the castanospermines, compounds of proven biological activity,[7] could be obtained using polyhydroxylated thiocanes.

Another application of this general method is the synthesis of enantiomerically pure polyhydroxylated sulfurated cycles. These compounds have recently been the subject of much interest[8,9] with regard to their use in nucleoside analogues,[10] since they demonstrate potent antiviral activity. Enantiopure $C_2$-symmetric polyhydroxylated thiepanes **3**, **4**,[8] and **5**[8] (Figure 2) were synthesized from D-mannitol, following known procedures, and were then subjected to the transannular cyclization reaction as previously described ($Me_3SiCl$/NaI/MeCN/reflux).[1]

The reaction of $Me_3SiI$ with 4(*R*),5(*R*)-dihydroxythiepane (**3**) was assumed to proceed by ring contraction of a 7-membered to a 5-membered cyclic sulfide through the oxonium intermediate **6** (Scheme 1), which led to the 1-thioniabicyclo[3.2.0]heptane intermediate (**7**) by means of the transannular sulfide interaction and displacement of the OH group coordinated with the silicon reagent. The intermediate **7**, *via* iodide attack at the α position of the 4-membered ring moiety, gave the (2*S*,3*R*)-2-(2-iodoethyl)-3-hydroxytetrahydrothiophene (**8**) in 97% yield (Scheme 1). This optically pure compound represents a precursor to various derivatives: the iodide could be exchanged with a hydroxy group[8] and the homologs at the side chain are easily accessible. Moreover, by reductive desulfurization, using experimental conditions that avoid racemization,[11] 3*R*-alcohols can be obtained. This methodology was used to synthesize enantiomerically pure 3(*R*)-hexanol (**9**)[12] from **8** in 80% yield.

In substrates **4** and **5**, the transannular attack at $C_3$ or $C_4$ could lead to a mixture of polyhydroxylated tetrahydrothiopyrans or tetrahydrothiophenes.

It has recently been reported[8] that, by the ring contraction reaction achieved under Mitsunobu conditions on substrates analogous to ours, only one product or a mixture of products were obtained, depending on the stereochemistry of the starting material and the substrate:reagent ratio.

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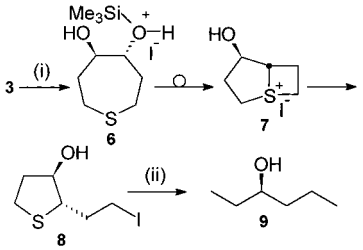
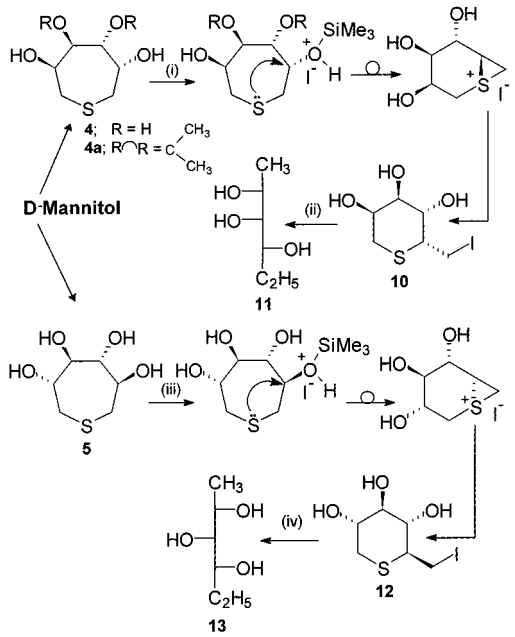
**Scheme 1**[a]



[a] (i) $Me_3SiI$, $CH_3CN$, 15 min reflux (97%); (ii) Raney Ni (W-2), $NaH_2PO_2$, pH 5.2, 1 h reflux (80%).

**Scheme 2**[a]



[a] (i) $Me_3SiI$, $CH_3CN$, 3 h rt (97%); (ii) Raney Ni (W-2), $NaH_2PO_2$, pH 5.2, 1 h reflux (84%); (iii) $Me_3SiI$, $CH_3CN$, 6 h reflux (88%); (ii) Raney Ni (W-2), $NaH_2PO_2$, 5 h reflux (84%).

By means of a very simple methodology, based on the use of $Me_3SiI$, **10** and **12** were obtained exclusively (free of any 5-membered cyclic sulfides) from **4** (or **4a**) and **5**, respectively through a 7- to 6-membered ring contraction reaction. In both cases, as predictable for an $S_N2$ transannular cyclization and due to the presence of a $C_2$-symmetric axis (Scheme 2), only one diastereoisomer was obtained.

There is evidence that episulfonium salt is formed by a stereo- and regio-specific process, followed by a ring contraction toward the more stable tetrahydrothiopyran derivative which occurs independently from the substrate:reagent ratio.

The results are consistent with the exclusive formation of the [4.1.0] bicyclic intermediate, although, as we previously found for **3**, the formation of a [3.2.0.] sulfonium salt intermediate could also be possible. On the other hand, in the case of acyclic hydroxy sulfides, evidence has been found,[1] using labeled compounds, for the exclusive formation of a thiiranium and not a thietanium intermediate from 1,3- and 1,4- hydroxy sulfides.

Under the experimental conditions used, compounds **4** and **4a** cyclize considerably more readily (3 h at rt, 98% yield) than **5** (6 h at 90 °C, 88% yield). This can be explained on the basis of the transition state for the intramolecular $S_N2$ reaction requiring the sulfur atom, the oxonium leaving group, and the carbon center to be approximately collinear, a conformation which Dreiding stereomodels suggest to be considerably more strained for **5** than for **4** or **4a**. In particular, if **5** is protected at hydroxy groups on $C_4$ and $C_5$ by a bulky group (acetonide) the reaction does not occur.

The formation of a 6-membered sulfurated ring, confirmed by spectroscopic data, also emerges from the conversion (by reductive desulfurization with the Raney Ni system) of **10** and **12** into the enantiomerically pure alcohols **11** and **13**, respectively. These latter compounds, which differ in configuration at $C_2$, are not known in the literature, and more generally, there is no synthetic methodology for hexantriols which permits a complete configurational control at the different chiral centers.

In conclusion, the reaction described is interesting on several accounts: (1) the reaction is completely stereo- and regiospecific; however, the direction of the attack appears to depend on the position of the hydroxy group in the ring and on the size of the potentially formed ring; (2) the reaction products are enantiopure synthons which may be usefully elaborated toward valuable synthetic targets using, as the starting material, D-mannitol, a readily available and inexpensive sugar; (3) the transannular cyclization is promoted by $Me_3SiI$, a mild reagent compatible with a variety of functional groups.

Our synthetic approach could be further extended to linear systems, polyhydroxylated thiepanes derived from different sugars not only $C_2$-symmetric and medium-sized polyhydroxylated cyclic sulfides.

## Experimental Section

**General.** All moisture sensitive reactions were performed in flame-dried glassware equipped with rubber septa under positive pressure of dry nitrogen. Organic extracts were dried over $CaSO_4$. Thin-layer chromatography was performed on Merck Kieselgel 60 $F_{254}$, the spots being developed at 110 °C with an aqueous solution of $(NH_4)_6Mo_7O_{24}$ (2.5%) and $(NH_4)_4$-$Ce(SO_4)_4$ (1%) in 10% $H_2SO_4$ or $KMnO_4$ 0.1 M/$H_2SO_4$ 1 M 1/1. Preparative flash chromatographic separations were performed using ICN Silica Adsorbienten, 230−400 mesh. $^1H$ and $^{13}C$ spectra were recorded at 200 and 50.3 MHz, respectively. Chemical shifts, unless otherwise specified, were measured in $\delta$ and referenced to $CDCl_3$ (7.25 ppm for $^1H$ NMR and 77.2 ppm for $^{13}C$ NMR). Signal multiplicities were established by DEPT experiments. The assignments were confirmed, if necessary, by 2D-NMR (COSY and HETCOR). Solvents were reagent grade and were obtained dry as follows: tetrahydrofuran (THF) was distilled from benzophenone ketyl; $CH_3CN$ and $CH_2Cl_2$ were refluxed over and distilled from $CaH_2$ then stored over molecular sieves (3Å); pyridine was distilled from KOH and $CH_3OH$ from Mg. Chlorotrimethylsilane was purified by distillation under nitrogen just prior to use. NaI was heated at 100 °C and 0.1 mmHg for 48 h.

**(4*R*,5*R*)-(−)-Dihydroxythiepane (3).** (1*R*,7*R*)-(−)-9,9-Dimethyl-8,10-dioxa-4-thiabicyclo[5.3.0]decane[13] (1.88 g, 10 mmol) was heated with 9 mL of 0.1 N aqueous $H_2SO_4$ and 25 mL of dioxane at 95 °C for 3 h, acetone was distilled as an azeotropic mixture (acetone, water, dioxane), and dioxane was added regularly to restore the solvent. The solution was neutralized by $NaHCO_3$, filtered, dried, and evaporated. The product was distilled (bp 145 °C/0.5 mmHg) to give 1.39 g (93.9%) of the title compound. $^1H$ NMR, $\delta$: 3.60 (m, 2H, CHO), 3.44 (brs, 2H, 2OH), 2.65 (m, 4H, $CH_2S$), 2.28 (m, 2H), 1.82 (m, 2H).$^{13}C$ NMR, $\delta$: 76.1 (CH), 35.6 ($CH_2S$), 26.4 ($CH_2$). $[\alpha]^{27}_D = -11.3$ ($c = 2.01$, $CHCl_3$);

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$[\alpha]^{27}_D = -12.8$ ($c$ = 2.04, $C_2H_5OH$ abs). Anal. Calcd for $C_6H_{12}O_2S$: C, 48.62; H, 8.16. Found: C, 48.60; H, 8.15.

**Reaction of Polyhydroxylated Cyclic Sulfides with $Me_3SiCl/NaI$.** Sodium iodide (1.1 mmol) was added to 10 mL of a 0.1 M acetonitrile solution of the substrate, followed by 1.1 mmol of freshly distilled $Me_3SiCl$, added dropwise. Reaction times and temperatures are reported for each product below. At rt, a few drops of 10% $NH_4Cl$ were added, followed by $CH_2Cl_2$ extraction. The organic layer was dried and evaporated. The iodo derivatives obtained were used, without any further purification, for the reductive desulfurization. The nature of products was determined by $^1H$- and $^{13}C$ NMR.

***exo*-4-Hydroxy-*cis*-1-thioniabicyclo[3.3.0]octane Iodide (2).**[6] Compound **1** was refluxed for 3 h to give the title compound in 85% yield. $^{13}C$ NMR (acetone-$d_6$), $\delta$: 78.7 ($C_4$), 73.7 ($C_5$), 45.8 ($C_8$), 42.0 ($C_2$), 35.5 ($C_3$), 32.7 ($C_6$), 30.2 ($C_7$).

**(2*S*,3*R*)-2-(2-Iodoethyl)-3-hydroxytetrahydrothiophene (8).** Compound **3** was refluxed for 15 min to give the title compound in 97% yield. $^1H$ NMR (acetone-$d_6$), $\delta$: 4.20−3.70 (brs, 1H, OH), 3.40−3.12 (m, 4H), 2.93−2.62 (m, 2H), 2.33−2.15 (m, 1H), 2.05−1.85 (m, 2H), 1.80−1.62 (m, 1H). $^{13}C$ NMR (acetone-$d_6$), $\delta$: 79.2 (CHO), 56.5 (CHS), 40.7, 37.4, 28.1 ($3CH_2$), 5.1 ($CH_2I$).

**(2*R*,3*S*,4*R*,5*S*)-2-(Iodomethyl)-3,4,5-trihydroxytetrahydrothiopyran (10).** Compound **4** or **4a** was submitted to reaction at rt for 3 h to give **10** in 97% yield. $^1H$ NMR (methanol-$d_4$), $\delta$: 4.05 (dd, 1H, CHO, $J$ = 4.97, 1.18 Hz), 3.93 (ddd, 1H, CHO, $J$ = 11.09, 4.12, 2.65 Hz), 3.70 (m, 1H, CHO), 3.33−3.12 (m, 3H, CH and $CH_2I$), 2.88 (dd, 1H, $CH_2S$, $J$ = 12.59, 11.13 Hz), 2.12 (dd, 1H, $CH_2S$, $J$ = 12.49, 4.06 Hz). $^{13}C$ NMR (methanol-$d_4$), $\delta$: 77.4, 73.0, 68.5 (3CHOH), 44.0 (CHS), 29.3 ($CH_2S$), 4.2 ($CH_2I$).

**(2*S*,3*S*,4*R*,5*R*)-2-(Iodomethyl)-3,4,5-trihydroxytetrahydrothiopyran (12).** Compound **5** was submitted to reaction for 6 h at rt, to afford **12** in 88% yield. $^1H$ NMR (methanol-$d_4$), $\delta$: 3.45−3.68 (m, 3H, C*H*$CH_2S$ and $CH_2I$), 3.33 (m, 1H, C*H*CHS), 3.18 (m, 1H, CHO), 2.67 (m, 2H, $CH_2S$), 2.54 (m, 1H, CHS, $J$ = 9.01 Hz). $^{13}C$ NMR (methanol-$d_4$), $\delta$: 88.4 (CHO), 77.8 (*C*HCHS), 75.1 (*C*H$CH_2S$), 48.9 (CHS), 33.6 ($CH_2S$), 7.8 ($CH_2I$).

**Reductive Desulfurization.**[11] To a solution of sulfide (0.30 mmol) in an acetate buffer (pH 5.2) and ethanol (1:2.9 mL) was added freshly prepared Raney Ni (W-2) (suspension in ethanol, 5 mL), followed by the addition of sodium hypophosphite monohydrate (321 mg, 3.0 mmol, in 2 mL water solution), the resultant suspension was refluxed to complete the reaction. The reaction mixture was filtered through Celite, dried, evaporated, and purified. Reaction times, purifying methods, and yields of the desulfurizated compounds are reported for each compound below.

**(−)-3*(R)*-Hydroxyhexane (9).** Compound **8** was submitted to reaction at reflux for 1 h, and the title compound was purified by distillation (bp 135 °C) and obtained in 80% yield. $^1H$ NMR, $\delta$: 3.52 (brs, 1H, OH), 0.92 (2t superimposed, 6H, $2CH_3$, $J$ = 7.48 Hz), 1.60−1.33 (m, 7H). $^{13}C$ NMR, $\delta$: 73.0 (CH), 39.0, 30.0, 18.6 ($3CH_2$), 13.9 ($CH_3CHO$), 9.6 ($CH_3CH_2$). $[\alpha]^{25}_D = -7.08$ ($c$ = 2.03, $CHCl_3$). Anal. Calcd for $C_6H_{14}O$: C, 70.53; H, 13.81. Found: C, 70.50; H, 13.84.

**(−)-2*(R)*,3*(R)*,4*(R)*-Trihydroxyhexane (11).** Compound **10** was submitted to reaction at reflux for 1 h. The title compound, obtained in 84% yield, was purified by flash chromatography (ethyl acetate). $^1H$ NMR ($D_2O$), $\delta$: 3.91 (m, 1H, C*H*$CH_3$, $J$ = 6.23, 6.60 Hz), 3.65 (m, 1H, C*H*$CH_2$, $J$ = 6.33, 3.66 Hz), 3.23 (m, 1H, CHO, $J$ = 6.35, 3.66 Hz), 1.50 (m, 2H, $CH_2$, $J$ = 7.35, 6.28 Hz), 1.22 (d, 3H, C*H*$_3$CH, $J$ = 6.23 Hz), 0.93 (t, 3H, C*H*$_3$-$CH_2$, $J$ = 7.37 Hz).$^{13}C$ NMR ($D_2O$), $\delta$: 79.3, 74.9, 70.2 (3CHO), 28.5 ($CH_2$), 20.7 ($CH_3CH$), 12.3 ($CH_3CH_2$). $[\alpha]^{28}_D = -4.0$ ($c$ = 1.5, $CH_3OH$). Anal. Calcd for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.73; H, 10.55.

**(−)-2(*S*),3(*R*),4(*R*)-Trihydroxyhexane (13).** Compound **12**, submitted to reaction at reflux for 5 h, gave the title compound in 84% yield and was purified by flash chromatography (ethyl acetate). $^1H$ NMR (methanol-$d_4$), $\delta$: 3.84 (m, 1H, C*H*$CH_3$, $J$ = 6.38, 5.09 Hz), 3.71 (m, 1H, C*H*$CH_2$, $J$ = 7.90, 5.43, 3.20 Hz), 3.19 (dd, 1H, CHO, $J$ = 5.04, 3.34 Hz), 1.54 (m, 2H, $CH_2$, $J$ = 7.44 Hz), 1.38 (d, 3H, C*H*$_3$CH, $J$ = 6.38 Hz), 1.15 (t, 3H, C*H*$_3$-$CH_2$, $J$ = 7.45 Hz). $^{13}C$ NMR (methanol-$d_4$), $\delta$: 78.1, 75.0, 70.1 (3CHO), 28.0 ($CH_2$), 20.2 ($CH_3CH$), 10.9 ($CH_3CH_2$). $[\alpha]^{28}_D = +4.12$ ($c$ = 0.63, $CH_3OH$). Anal. Calcd for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.69; H, 10.53.

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